RLL-1.1US

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Talwar et al.	Examiner: Todd Ware
Application No.:	09/347,315	Group Art Unit: 1615
Filing Date:	July 2, 1999	
For:	ORALLY ADMINISTERED CONTROLLED DRUG DELIVERY SYSTEM PROVIDING TEMPORAL AND SPATIAL CONTROL	

#19 Drugs 2/17/01

DECLARATION OF FACTS AND DATA SUBMITTED FOR CONSIDERATION AS PART OF INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, DC 22031

I, Tausif Monif, declare as follows:

(1) I am currently employed as "Group leader – Clinical Pharmacology and Pharmacokinetics" by Ranbaxy Research Laboratories, a division of Ranbaxy Laboratories Limited, the assignee of the present application (2000 March – Present)

(2) My educational qualifications are as follows: B. Pharm., Birla Institute of Technology, Ranchi, India (1983-1987); M. Pharm., Pharmaceutics, Birla Institute of Technology, Ranchi, India (1987-1989); and Ph.D., Pharmaceutics, Central Drug Research Institute, Lucknow, India (1989-1993)

(3) After obtaining my PhD in 1993, I have been employed by Ranbaxy Research Laboratories as "Senior Research Scientist – Clinical Pharmacology and Pharmacokinetics" up until March 2000.

(4) My duties at Ranbaxy have included the following: to lead a group of scientists to conduct Pharmacokinetic studies for generic dosage forms and new drugs in conformance to GCP/GLP guidelines; to draw out an yearly work plan of all biostudies for the department in consultation with the business groups, regulatory affairs, Product Deevlopment Research & Novel Drug Delivery Systems (NDDS); to draw our time lines for various tasks in a projects and people responsible for them; implementing quality systems in the bioanalytical laboratory and also monitoring, developing and training the laboratory personnel to generate reports of acceptable international standards.Provide technical input for upgradation of the analytical methodologies in the bioanalytical laboratory to expedite method development and validation activity for bioequivalence projects; reviewing bioanalytical data and provide pharmacokinetic evaluation in the assessment of products and dosage forms; acting as a study director and ensuring conformance to quality systems and to the successful initiation and completion of studies for generating bioequivalence reports; providing expert comments and review data on NDDS products; laising with Contract Research Organizations for negotiating prices and monitoring bioequivalence studies; ensuring initiation and completion of extramural bioequivalence studies as per business plans; reviewing progress of assigned projects and to give instructions to optimize resources; interacting with Contract Research Organizations on technical issues relating to bioavailability/bioequivalence studies.

(5) I have personal knowledge of the pharmacokinetic studies described below and was responsible, at least in part, for initiating the studies (excepting the studies detailed at Tables 1A and 1B, which formed part of the present patent application as filed). All

the statements made below in regards to the pharmacokinetic studies are made based on personal knowledge or are made based on information and belief.

(6) The values for Ciprofloxacin pharmacokinetic parameters described below were calculated using standard non-compartmental methods. Ciprofloxacin was measured in Serum / Plasma using a validated HPLC method.

Ciprofloxacin 500 mg OD

Table 1A and 1B summarises the pharmacokinetic results obtained after dosing of Ciprofloxacin 500 mg OD immediately after administration of a high fat or a normal meal as a single dose administration or a multiple dose administration. The immediate release Cipro™ 250 mg tablets were tested under both fed and fasted conditions.

In all the above studies the OD formulation gave serum concentration time profiles desirable for once daily dosage form in that the peak serum concentration Cmax or Cmaxss was comparable to that for the immediate release drug indicating a similar rate of absorption of the drug. The total bioavailability of the drug (AUC) was also comparable (Table 1A and 1B).

The AUC above MIC values at a level of 0.5 mcg/mL for Ciprofloxacin OD 500 mg vs Cipro™ 250 mg b.i.d were better for Cipro OD 500 mg than those for Cipro™ immediate release tablets administered twice daily under fed or fasting conditions, indicating better therapeutic efficacy of the OD formulation (Table 1A and 1B).

The Summary results of another study conducted on 500 mg OD at a Contract Research Organisation (United States) are also attached (Table 1C and 1D). However, the results derived from the data were not consistent with studies carried out as described above. There is no known explation for the inconsistent results.

Ciprofloxacin 1000 mg OD

Table 2A and 2B summarises the pharmacokinetic results obtained after dosing of Ciprofloxacin 1000 mg OD immediately after administration of a high fat or a normal meal as a single dose administration or a multiple dose administration. The immediate release Cipro™ 500 mg tablets were tested under both fed and fasted conditions.

Ciprofloxacin was measured in Serum / Plasma using a validated HPLC method.

In all the above studies the OD formulation gave serum concentration time profiles desirable for once daily dosage form in that the peak serum concentration Cmax or Cmaxss was comparable to that for the immediate release drug indicating a similar rate of absorption of the drug. The total bioavailability of the drug (AUC) was also comparable (Table 2A and 2B).

The AUC above MIC values at a level of 1.0 mcg/mL for Ciprofloxacin OD 1000 mg vs Cipro™ 500 mg b.i.d were better for Cipro OD 1000 mg than those for Cipro™ immediate release tablets administered twice daily under fed or fasting conditions, indicating better therapeutic efficacy of the OD formulation (Table 2A and 2B).

The summary results of another study conducted on 1000 mg OD product at a Contract Research Organisation (United States) are also attached (Table 2C and 2D). However, the results were not consistent with studies carried out as described above. There is no known explanation to these inconsistent results.

Table 1A

CIPROFLOXACIN 500 MG OD

Study No.	Product	Dose	Number of Subjects	Arithmetic Mean Cmax (mcg/mL)	Arithmetic Mean AUC0-t (mcg.h/mL)	Arithmetic Mean AUC>MIC 500 ng/mL (mcg.h/mL)
185/00 (Day 1)*	Ciprofloxacin OD 500 mg Fed [500 Kcal Meal]	500 mg OD	24	1.03	5.69	0.97
	Ciprofloxacin OD 500 mg Fed [FDA Meal]	Multiple Dose		0.84	6.01	0.69
	Ciprofloxacin 250 mg b.i.d [Fasted]			0.97	6.43	0.76
185/00 Steady State (Day 5)*	Ciprofloxacin OD 500 mg Fed [500 KCal Meal]	500 mg OD	22	1.04	6.67	1.24
	Ciprofloxacin OD 500 mg Fed [FDA Meal]	Multiple Dose		0.85	7.29	1.07
	Ciprofloxacin 250 mg b.i.d [Fasted]			1.22	8.04	1.25

Table 1B

CIPROFLOXACIN 500 MG OD

Study No.	Product	Dose	Number of Subjects	Arithmetic Mean Cmax (mcg/mL)	Arithmetic Mean AUC0-t (mcg.h/mL)	Arithmetic Mean AUC>MIC 500 ng/mL (mcg.h/mL)
100295**	Ciprofloxacin OD 500 mg Fed [500 KCal Meal]	500 mg OD	34	1.42	8.59	2.45
	Ciprofloxacin 250 mg b.i.d. [500 KCal Meal]	Single Dose		0.90	8.08	1.01
	Ciprofloxacin 250 mg b.i.d [Fasted]			1.24	10.12	2.06

*Location (Clinical & Analytical): Ranbaxy, India
**Location (Clinical & Analytical): NDS Pharma Services, Lincoln, Nebraska

Table 1C

CIPROFLOXACIN 500 MG OD

Study No.	Product	Dose	Number of Subjects	Arithmetic Mean Cmax (mcg/mL)	Arithmetic Mean AUC0-t (mcg.h/mL)
100240 (Day 1)*	Ciprofloxacin OD 500 mg Fed [500 KCal Meal]	500 mg	36	1.04	6.59
	Ciprofloxacin OD 500 mg Fed [FDA Meal]	Multiple Dose		0.86	7.27
100240 Steady State (Day 5)*	Ciprofloxacin OD 500 mg Fed [500 KCal Meal]	500 mg	36	1.03	6.56
	Ciprofloxacin OD 500 mg Fed [FDA Meal]	Multiple Dose		1.00	7.74
	Ciprofloxacin 250 mg b.i.d [Fasted]			1.49	10.51

Table 1D

CIPROFLOXACIN 500 MG OD

Study No.	Product	Dose	Number of Subjects	Arithmetic Mean Cmax (mcg/mL)	Arithmetic Mean AUC0-t (mcg.h/mL)
100239**	Ciprofloxacin OD 500 mg Fed [500 KCal Meal]	500 mg	36	0.77	6.06
	Ciprofloxacin OD 500 mg [Fasted]	Single Dose		0.56	2.95
	Ciprofloxacin 250 mg b.i.d [Fasted]			1.34	9.51

*Location: Clinic : Clinical Pharmacology Associates, Miami

Table 2A

CIPROFLOXACIN 1000 MG OD

Study No.	Product	Dose	Number of Subjects	Arithmetic Mean Cmax (mcg/mL)	Arithmetic Mean AUC0-t (mcg.h/mL)	Arithmetic Mean AUC>MIC 1 mcg/mL (mcg.h/mL)
79/98*	Ciprofloxacin 500 mg [FDA Meal]	1000 mg OD	12	2.7	20.0	4.5
	Ciprofloxacin 500 mg [Fasting]	Single Dose		3.2	24.0	7.5
	Ciprofloxacin 1 g [FDA Meal]			3.0	23.1	7.6
197/00*	Ciprofloxacin OD 1 g Fed [500 KCal Meal]	1000 mg OD	23	2.30	13.29	2.91
	Ciprofloxacin 500 mg b.i.d.[Fasted]	Single Dose		2.26	16.20	2.95

Table 2B

CIPROFLOXACIN 1000 MG OD

Study No.	Product	Dose	Number of Subjects	Arithmetic Mean Cmax (mcg/mL)	Arithmetic Mean AUC0-t (mcg.h/mL)	Arithmetic Mean AUC>MIC 1 mcg/mL (mcg.h/mL)
100294**	Ciprofloxacin OD 1 g Fed [500 KCal Meal]	1000 mg OD	29	2.47	15.92	3.81
	Ciprofloxacin 500 mg b.i.d.Fed [500 KCal Meal]	Single Dose		1.70	16.96	2.16
	Ciprofloxacin 500 mg b.i.d [Fasted]			2.17	19.34	3.60

Table 2C

CIPROFLOXACIN 1000 MG OD

Study No.	Product	Dose	Number of Subjects	Arithmetic Mean Cmax (mcg/mL)	AUC0-t (mcg.h/mL)	AUC>MIC 1 mcg.h/mL (mcg.h/mL)
100221 (Day 1)*	Ciprofloxacin OD 1 g Fed [500 KCal Meal]	1000 mg OD	36	2.71	17.94	8.24
	Ciprofloxacin OD 1 g Fed [FDA Meal]	Multiple Dose		2.72	26.02	10.09
100221 Steady State (Day 5)*	Ciprofloxacin OD 1 g Fed [500 KCal Meal]	1000 mg OD	36	2.57	16.83	5.10
	Ciprofloxacin OD 1 g Fed [FDA Meal]	Multiple Dose		2.54	25.37	8.58
	Ciprofloxacin 500 mg b.i.d [Fasted]			3.11	28.01	14.64

Table 2D

CIPROFLOXACIN 1000 MG OD

Study No.	Product	Dose	Number of Subjects	Arithmetic Mean Cmax (mcg/mL)	AUC0-t (mcg.h/mL)	AUC>MIC 1 mcg.h/mL (mcg.h/mL)
100220**	Ciprofloxacin OD 1 g Fed [500 KCal Meal]	1000 mg OD	35	2.24	18.92	N/A
	Ciprofloxacin OD 1 g [Fasted]	Single Dose		1.39	7.36	N/A
	Ciprofloxacin 500 mg b.i.d [Fasted]			2.17	19.59	N/A

*Location: Clinic : Phoenix, Cincinnati

Analysis: Clinical PK Laboratory, Millard, Fillmore Hiospital, Buffalo, NY

**Location: Clinic : Phoenix, Cincinnati

Analysis: Bayer, USA

Serial No. 09/347,315

I hereby declare that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these were made with the knowledge that willful false statements and the like so made are punishable under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any parent to which this verified statement is directed.

Tausif Monif

03 Nov 2000